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MULTIMODALITY TREATMENT APPROACH FOR LOCALLY ADVANCED PANCREATIC CANCER

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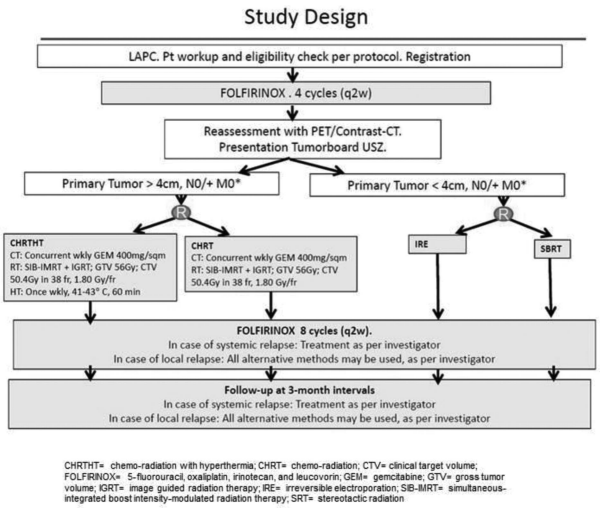
Introduction: Pancreatic cancer is the 7th leading cause of cancer-related death worldwide with 5-year survival rates of around 5%. Complete surgical resection is the only curative option but only 10-20% of patients are suitable for it. Probably micro-metastases at the time of diagnosis are responsible for the poor outcome even after R0 resection, no nodal involvement (pN0), and despite adjuvant treatment. In the last decade the prognosis of this illness has not changed much although some therapeutic improvements have been made. Adjuvant chemotherapy with gemcitabine had some effect on the one-year survival rate but efficacy is limited. FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan and leucovorin) has become the new standard in advanced disease. But there is only limited experience with FOLFIRINOX in both the neoadjuvant as well as the adjuvant setting. Therefore, prospective clinical trials are needed to investigate the benefit of intensified neoadjuvant and adjuvant chemotherapy regimens for locally advanced pancreatic cancer (LAPC). In addition, innovative local treatments like stereotactic body radiotherapy (SBRT), hyperthermia as well as irreversible electroporation (IRE) have been tried in pancreatic cancer with some promise. Similarly, these approaches should undergo more formal evaluation. Based on these considerations the following studies of a tandem approach to LAPC are being launched.

Methods: Trial Design



CHRTHT= chemo-radiation with hyperthermia; CHRT= chemo-radiation; CTV= clinical target volume; FOLFIRINOX= 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin; GEM= gemcitabine; GTV= gross tumor volume; IGRT= image guided radiation therapy; IRE= irreversible electroporation; SIB-IMRT= simultaneous-integrated boost intensity-modulated radiation therapy; SRT= stereotactic radiation

Pancreatic cancer resectability is defined by the absence of metastases and only limited invasion of arteries (SMA, common hepatic artery, celiac trunk) and veins (superior mesenteric vein / portal vein) (Katz et al. 2013, Ann Surg Oncol 20:2787). Only Stage III pancreatic cancer (AJCC – TNM 7th edition) will be enrolled in the study. All cases will be reviewed at the multidisciplinary meeting to confirm eligibility. After obtaining their informed consent patients will receive 4 cycles of FOLFIRINOX chemotherapy. Following reassessment, patients without progression will proceed to local treatment. Diagnostic laparoscopy will be performed to exclude distant metastases. Unresectable tumors up to 4cm will be randomized between stereotactic body radiotherapy (SBRT) (Arm A) versus irreversible electroporation (IRE) (Arm B). Tumors larger than 4cm will be randomized to chemo-radiation (Intensity modulated radiation therapy: $28 \times 2Gy = 56$ Gy to the primary tumor and metastatic lymph nodes, 28×1.8 Gy = 50.4 Gy to the elective nodal area along with gemcitabine 400mg/m^2 weekly) (Arm C) versus the same in combination with hyperthermia (weekly hyperthermia at 41-43°C over 60min, given 24 hours after gemcitabine) (Arm D). Patients developing metastases or local progression, forbidding continuation of protocol treatment will go off study at any time. One month following local treatment, adjuvant chemotherapy with FOLFIRINOX will be resumed for 8 cycles. Statistical considerations: The expected 1-year survival rate is 50% (p0) and we expect a clinically relevant difference of +20% (Arms A vs B; Arms C vs. D). Sample size based on Simon's two-stage minimax design with one-sided alpha 0.05 and power of 80%, drop-out rate 10%, is between 24 to 40 per arm; i.e. a total of 96 to 160 patients for the whole program.